Original Article

https://doi.org/10.22491/2357-9730.98431

Federal university hospitals: heterogeneity in the coordination of clinical trials authorized by the National Health Surveillance Agency

Claudia Simone Costa da Cunha[1], Olimpio J Nogueira V Bittar[2], Beatriz H Tess[3]

Clin Biomed Res. 2020;40(2):76-83.

1 Consultora Instituto Israelita Albert Einstein, Sociedade Beneficente Israelita Brasileira Albert Einstein (SBIBAE). São Paulo, SP, Brasil.

2 Gabinete do Secretário, Secretaria de Estado da Saúde de São Paulo (SES-SP). São Paulo, SP, Brasil.

3 Departamento de Medicina Preventiva, Faculdade de Medicina, Universidade de São Paulo (USP). São Paulo, SP, Brasil.

Corresponding author:
Claudia Simone Costa da Cunha
claudia.sccunha@gmail.com
Sociedade Beneficente Israelita Brasileira Albert Einstein (SBIBAE)
Avenida Albert Einstein, 627/701
05652-900, São Paulo, SP, Brasil.

ABSTRACT

Introduction: This study aimed to describe clinical trials approved by the Brazilian Health Surveillance Agency (ANVISA) and coordinated by federal university hospitals (FUHs), as well as to investigate the relationship between the number of clinical trials and the assistance provided by these FUHs.

Methods: This is a cross-sectional study based on data obtained from the ANVISA clinical trial consultation system. The National Register of Health Care Facilities and the Ambulatory Care Information System of the Unified Health System (SUS) were used as sources of information on the assistance provided by FUHs, such as the mean number of specialized medical consultations and the number of beds. Scatter plot and Spearman's correlation coefficient analyses were used to verify the association between these aspects of FUHs and the number of clinical trials.

Results: Between 2012 and 2013, ANVISA authorized 209 trials to be coordinated by 23 FUHs; 75% of the trials were coordinated by 7 FUHs, 69.8% were phase III trials, and 94% were multicenter studies. The number of clinical trials presented positive and statistically significant associations with the mean number of specialized medical consultations and the number of beds (Spearman's correlation coefficients r = +0.70 and r = +0.64, respectively).

Conclusion: FUHs have a leadership role in the conduction of clinical trials in Brazil, but showed heterogeneity regarding their assistance capacities and the number of clinical trials. A predominance of phase III trials may be interpreted as a low use of the scientific potentiality of these facilities.

Keywords: *University hospitals; teaching hospitals; clinical trial; Brazilian Health Surveillance Agency*

INTRODUCTION

Federal university hospitals (FUHs) are part of federal universities and are committed to a tripartite mission of health care, research, and teaching. Their financial sources are the Brazilian Ministries of Health and Education[1]. In 2011, the federal government created the Brazilian Company of Hospital Services (EBSERH), a government-sponsored enterprise, to improve management and increase and qualify the workforce of these hospitals[2]. In 2013, there were 47 FUHs linked to 35 federal universities, of which 21 had an agreement with EBSERH[3]. In 2019, out of 50 FUHs linked to 35 federal universities, 40 had EBSERH participating in their management.

FUHs represent 2% of the national public hospital network and account for 3.3% of the beds available in the Unified Health System (SUS)[4]. According to the Directory of Research Groups of the National Council for Scientific and Technological Development (CNPq), approximately half of the current research groups in health sciences are based in federal universities and their hospitals[5].

ISSN 2357-9730

Clinical trials involve research using human volunteers for testing the efficacy and safety of interventions using medical products, such as drugs or devices, or changes to participants' behaviors, such as diets. These studies aim to produce scientific knowledge to improve health care. These types of studies are classified according to the phase of development of the interventions being studied. Phase I trials assess product safety in healthy individuals; phase II trials analyze the safety and efficacy of the product by comparison to another product or a placebo within a small and homogeneous group of individuals with the disease under study; phase III trials repeat this assessment in a larger and more varied group of sick individuals; finally, phase IV trials are performed after commercialization and monitor adverse effects or events[6].

Many clinical trials are performed in FUHs and their protocols and results are among the documents required by regulatory bodies to support the decision on its registration. The approval of clinical trials with the aim of registering drugs and products for commercialization in Brazil is subject to the authorization of the Brazilian Health Surveillance Agency (ANVISA)[7], the institution's Research Ethics Committee (CEP), and the National Commission of Ethics in Research of the National Health Council (CONEP/CNS)[8].

According to ClinicalTrials.gov, around 311 000 clinical trials were registered worldwide from 1997 to 2019. North American studies corresponded for 44% of these trials, European trials represented 29%, East Asian studies accounted for 11%, and South American studies were 3.2%. Brazil hosted 70% of approximately 10,000 registered clinical trials in South America, representing 2.3% of the global total[9]. Industry Standard Research reports indicate that global investments on clinical research in 2018 were of around US$ 124 billion and should reach almost US$ 133 billion in 2021[10].

In 2014, the EBSERH Strategic Clinical Research Program for SUS (EpecSUS) was created for implementing a model for clinical research management within FUHs[11]. This program was expected to promote the institutionalization, transparency, and effectiveness of the trial approval process, as well as the development, budgetary execution, and monitoring of clinical research in compliance with Good Clinical Practices (GCP)[12]. EpecSUS also aimed to promote clinical research considering themes that were strategic for the SUS.

Our study aimed to describe the clinical trials approved by ANVISA to be coordinated by FUHs and to investigate the association between the number of clinical trials and the assistance provided by these FUHs.

METHODS

This is a cross-sectional, retrospective study that used information retrieved from the ANVISA clinical trial consultation system. This system can be accessed by filling at least two of the following fields: protocol title, protocol code, name of drug or product under study, disease for which the drug or product will be prescribed (following the International Statistical Classification of Diseases and Related Health Problems, 10th revision [CID-10]), date of trial authorization, process number, and Special Notice number[13].

With the collaboration of ANVISA's Clinical Research Management (GEPEC), EBSERH obtained the titles of clinical trials authorized to be coordinated by FUHs from January 1, 2012 to December 31, 2013. Searching the database by title and date of authorization, we obtained the therapeutic class of the tested product, CID-10, protocol code, and phase of the clinical trial.

The FUH service was assessed according to the numbers of beds and specialized medical consults conducted in 2012 and 2013. These data were collected from the National Register of Health Care Facilities (CNES) and the SUS Ambulatory Care Information System/Tabwin (SIA)[14] between October and December 2014.

Data were described by means of absolute and relative frequencies, standard deviations, and variation coefficients. An association between the number of clinical trials and the assistance provided by FUHs was investigated through a scatter plot and the Spearman's correlation coefficient test; statistical significance considered $p < 0.05$.

This study was based on secondary and public domain data; therefore, it was not submitted to a CEP in accordance with the CNS Resolution No. 466/2012[8].

RESULTS

According to GEPEC/ANVISA, 209 clinical trials (95 in 2012 and 114 in 2013) were authorized for conduction in 23 FUHs. These trials corresponded to 45% of all trials approved by ANVISA in this 2-year period. Out of these 23 hospitals, 7 were responsible for the coordination of three-quarters (n = 157) of the authorized trials.

Table 1 presents the selected metrics of hospital care and the number of clinical trials authorized per hospital. The number of beds varied from 15 to 687 (mean: 312), and the mean number of specialized medical consultations was 178 000, ranging from 8190 and 1 020 000. Each FUH coordinated up to 34 trials (mean: 9). The characteristics of the analyzed hospitals were highly heterogeneous.

Table 1: Federal university hospitals: numbers of beds and specialized medical consultations compared to the number of clinical trials authorized by the Brazilian Health Surveillance Agency (ANVISA) between 2012 and 2013.

Hospital*	No. of beds	No. of specialized consultations 2012	No. of specialized consultations 2013	No. of clinical trials
HCPA/UFRGS	*687*	*374 177*	*406 424*	*34*
HC/UFPR	*474*	*352 001*	*337 216*	*29*
HC/UFG	*384*	*125 595*	*146 178*	*21*
HSP/UNIFESP	*522*	*606 726*	*14 32992*	*21*
HC/UFMG	*511*	*245 382*	*257 122*	*19*
HUCFF/UFRJ	*471*	*239 047*	*216 168*	*18*
HUPES/UFBA	*353*	*19 1555*	*191 457*	*14*
HUGG/UNIRIO	*158*	*94 355*	*81 488*	*9*
HUJBB/UFPA	*284*	*99 945*	*83 685*	*8*
HUWC/UFC	*248*	*123 281*	*137 181*	*8*
HUB/UNB	*268*	*114 746*	*108 262*	*7*
HC/UFPE	*342*	*135 724*	*162966*	*4*
IP/UFRJ	*117*	*40 571*	*37 566*	*3*
HUCAM/UFES	*306*	*150 702*	*172 981*	*3*
HU/UFMA	*573*	*168 400*	*156 429*	*2*
HUMAP/UFMS	*257*	*80 925*	*72 007*	*2*
HUPEST/UFSC	*392*	*92 171*	*98 285*	*1*
HUAP/UFF	*256*	*145 797*	*154 450*	*1*
HE/UFTM	*299*	*122 114*	*109 928*	*1*
HU/UFJF	*140*	*76 508*	*84 269*	*1*
IPPMG/UFRJ	*69*	*49 283*	*51 443*	*1*
HESFA/UFRJ	*15*	*96 18*	*6 759*	*1*
INDC/UFRJ	*40*	*18 070*	*19 266*	*1*
Total				209

**HCPA/UFRGS: Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul; HC/UFPR: Hospital de Clínicas, Universidade Federal do Paraná; HU/UFG: Hospital Universitário, Universidade Federal de Goiás; HSP/UNIFESP: Hospital São Paulo, Universidade Federal de São Paulo; HC/UFMG: Hospital de Clínicas, Universidade Federal de Minas Gerais; HUCFF/UFRJ: Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro; HUPES/UFBA: Hospital Universitário Prof. Edgard Santos, Universidade Federal da Bahia; HUGG/UNIRIO: Hospital Universitário Gaffrée e Guinle, Universidade Federal do Estado do Rio de Janeiro; HUJBB/UFPA: Hospital Universitário João de Barros Barreto, Universidade Federal do Pará; HUWC: Hospital Universitário Walter Cantídio, Universidade Federal do Ceará; HUB/UNB: Hospital Universitário, Universidade de Brasília; HC/UFPE: Hospital das Clínicas, Universidade Federal de Pernambuco; IP/UFRJ: Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro; HUCAM/UFES: Hospital Universitário Cassiano A. de Moraes, Universidade Federal do Espírito Santo; HU/UFMA: Hospital Universitário, Universidade Federal do Maranhão; HUMAP/UFMS: Hospital Universitário Maria Aparecida Pedrossian, Universidade Federal de Mato Grosso do Sul; HUPEST/UFSC: Hospital Universitário Polydoro E. de São Thiago, Universidade Federal de Santa Catarina; HUAP/UFF: Hospital Universitário Antônio Pedro, Universidade Federal Fluminense; HE/UFTM: Hospital Escola, Universidade Federal do Triângulo Mineiro; HUJF/UFJJ: Hospital Universitário, Universidade Federal de Juiz de Fora; IPPMG/UFRJ: Instituto de Puericultura e Pediatria Martagão Gesteira, Universidade Federal do Rio de Janeiro; HESFA/UFRJ: Hospital Escola São Francisco de Assis, Universidade Federal do Rio de Janeiro; INDC/UFRJ: Instituto de Neurologia Deolindo Couto, Universidade Federal do Rio de Janeiro.*

Considering the numbers of specialized medical consultations and beds as metrics indicating hospital size, the scatter plot (Figure 1) illustrated a positive correlation between the number of clinical trials and the size of FUHs, that is, bigger hospitals coordinated more trials. The Spearman's correlation coefficient was $r = +0.64$ for the relationship between the numbers of beds and clinical trials. Regarding the relationship between the mean number of consultations and the number of clinical trials, the Spearman's correlation coefficient was $r = +0.70$. Both were statistically significant ($p < 0.05$).

All the evaluated clinical trials were conducted to assess the safety and efficacy of drugs. Figure 2 depicts the frequency distribution of drug therapeutic classes; this information was not available for 28 (13%) of the 209 clinical trials. Antineoplastic, antidiabetic, antiviral, and immunosuppressive drugs were the predominantly tested pharmacological groups. The therapeutic classes with frequencies smaller than 10 were grouped into the "other therapeutic classes" category, representing 49% of the evaluated clinical trials.

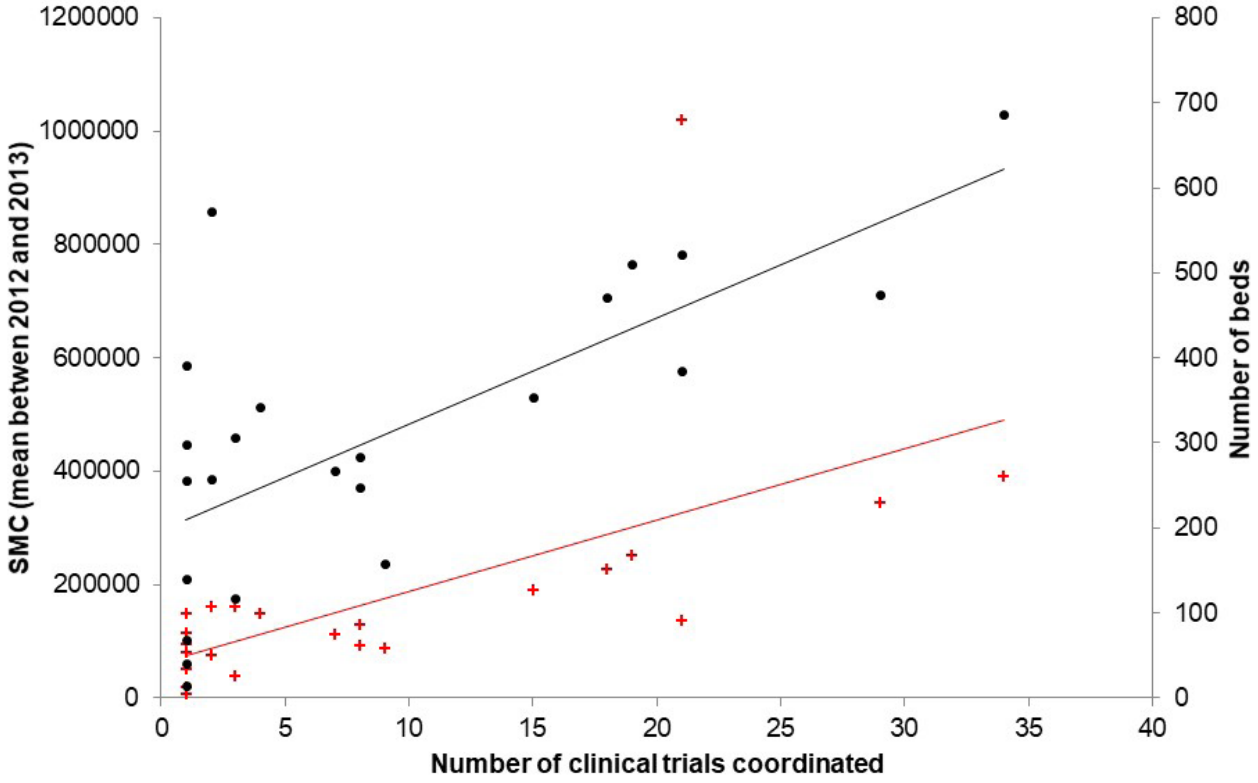

Figure 1: Correlation between number of clinical trials, specialized medical consultations, and number of beds

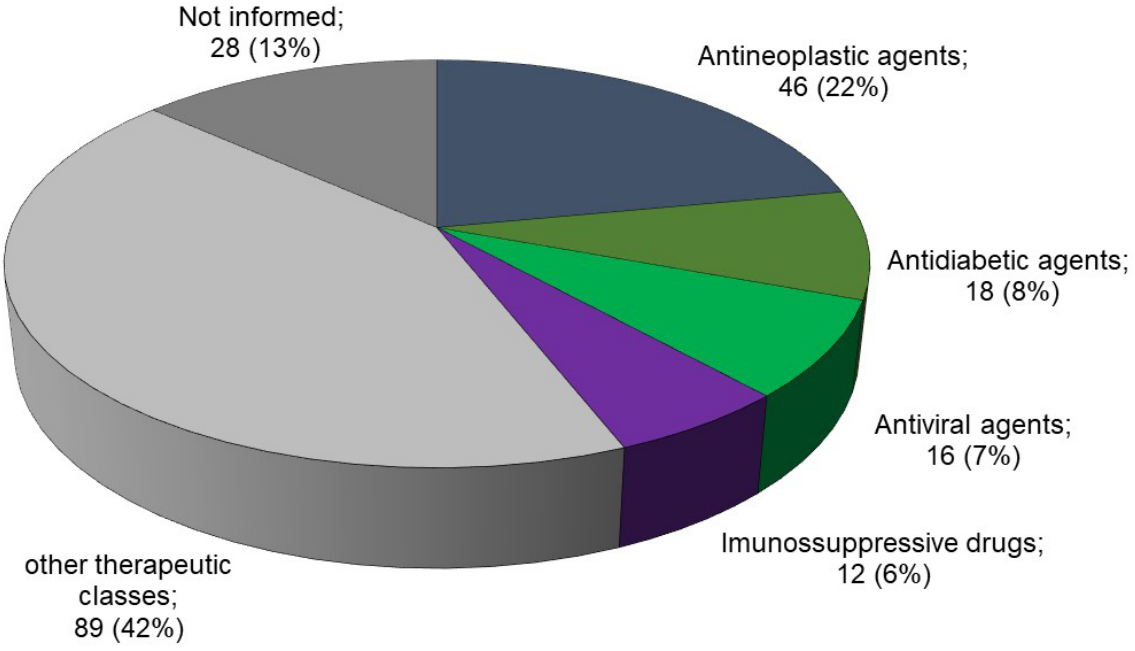

Figure 2: Frequency distribution of drug therapeutic classes

Table 2 shows the diseases (classified according to CID-10) for which the drugs were tested in 199 trials with available information. Endocrine diseases, neoplasms, and viral infections were the object of study in half of the clinical trials. Neoplasms, considering *in situ* and benign neoplasms, represented the most studied disease group (almost one-quarter of the trials).

The classification of clinical trials according to the phase of clinical development is presented in Table 3. We observed that the majority (69.8%) were phase III studies and 94% of the trials were multicenter. This information was not available for 10 of the evaluated trials.

Table 2: Number of clinical trials by groups of diseases targeted by the tested drugs.

Disease groups*	No.	(%)
A – Infectious Diseases: tuberculosis	1	(0.5)
B – Viral infections characterized by lesions of the skin and mucosa, hepatitis; human immunodeficiency virus disease	22	(11.1)
C – Neoplasms	40	(20.1)
D – *In situ* neoplasms and benign neoplasms	8	(4.0)
E – Nutritional and metabolic endocrine diseases	41	(20.6)
F – Mental disorders	7	(3.5)
G – Nervous system diseases	13	(6.5)
H –Diseases of the eye and its annexes	8	(4.0)
I – Circulatory system diseases	15	(7.5)
J – Respiratory system diseases	16	(8.0)
K – Digestive system diseases	3	(1.5)
L – Skin and subcutaneous tissue diseases	4	(2.0)
M – Diseases of the osteomuscular system and conjunctive tissue	14	(7.0)
N – Genitourinary system diseases	4	(2.0)
P – Affections of the perinatal period	2	(1.0)
Z – Factors that influence health conditions and the contact with health services	1	(0.5)
Total	199**	

*Disease groups according to the International Statistical Classification of Diseases and Health-Related Problems – 10th revision (CID-10).

**This information was not available for 10 of the clinical trials.

Table 3: Number of clinical trials according to their development phases.

Study phase	No.	(%)
I	3	(1.5)
II	31	(15.6)
III	139	(69.8)
IV	26	(13.1)
Total	199*	

*This information was not available for 10 of the clinical trials.

DISCUSSION

Even though FUHs account for a small fraction of the public health care network, they coordinated 45% of the clinical trials authorized by ANVISA between 2012 and 2013, playing an important role in the Brazilian process of registration and commercialization of new therapeutic products. We also found a significant heterogeneity in the number of trials per FUH. These trials most frequently studied endocrine and metabolic diseases, neoplasms, and viral infections, and the most assessed therapeutic classes of drugs were antineoplastic, antidiabetic, antiviral, and immunosuppressive medications. Our results also indicated that 94% of the trials were multicenter and most were phase III studies.

The central position of FUHs in the coordination of clinical trials has already been described by Quental & Salles. Their study reported that six FUHs coordinated 22% of 538 trials registered by 20 organizations[15]. The capacity of recruiting research participants and the presence of qualified professionals are characteristics that make institutions more competitive for clinical trials[15,16]. Considering that FUHs are distinct from other non-university hospitals or health services due to their research and teaching activities, their researchers' qualifications may explain why these institutions are highly sought to coordinate clinical trials despite their low participation in the national health care network. This hypothesis is further supported by the fact that the 4 FUHs that coordinated most clinical trials in our study were between the second and fifth positions of the national ranking of the CNPq Health Sciences Directory of Research Groups[5].

The coordination of 75% of the clinical trials was performed by 7 hospitals, which may be due to their capacity to recruit research participants. Overall, we found a positive relationship between the hospital assistance profile and the number of coordinated trials, but this relationship presented exceptions and a high heterogeneity. Some hospitals, such as Hospital Universitário da Universidade Federal do Maranhão, presented high values of assistance

metrics but coordinated only a small number of clinical trials, suggesting that other factors might influence the dominance of the 7 main hospitals.

In 2009, the Brazilian federal government provided financial support for the establishment of clinical research centers in public hospitals. This initiative aimed to increase the national capacity of conducting clinical research and included the creation of the National Clinical Research Network[17]. Among the FUHs analyzed in this study, 13 took part in this initiative. Further studies are needed to identify why some sponsored FUHs did not engage in research activities in this period or, conversely, conducted clinical trials without receiving these resources, such as Hospital de Clínicas da Universidade Federal do Paraná.

In addition, we have found a collaboration network among FUHs. This is an important finding and it is corroborated by the British experience, where the Clinical Research Network has supported and coordinated high-quality clinical investigations and facilitated the implementation of clinical trials in the scope of the National Health Services[18]. Functioning as a network may be an effective strategy to overcome challenges and barriers in patient recruitment. The adoption of this strategy has been proposed by EpecSUS[11], and this has been an ongoing process.

Our results also showed that the therapeutic classes of the studied drugs and the groups of target diseases were similar to those reported in other national[15] and international[19] studies. The development of drugs that treat progressive chronic diseases has been prioritized globally.

The stage of clinical development of the evaluated studies was mainly phase III (69.8%), followed by phases II (15.6%), IV (13.1%), and I (1.5%). This finding was in accordance with other national studies[15,20] that have shown the dominance of phase III studies. On the other hand, international studies have reported different distributions of stages of development. According to the analysis of 26 000 clinical trials registered in the European Federation of Pharmaceutical Industries and Associations between 2005 and 2010, 32% of these trials were phase I, 27% were phase II, and 21% were phase IV studies[21]. Phase III clinical trials are more frequent in middle-income countries, probably because they demand lower scientific density and present less technological risks; in addition, multinational drug companies usually prioritize phases I and II trials in their home countries[17]. We did not collect data regarding the sponsorship of the analyzed trials due to limitations of our search tool. However, other studies have reported that clinical trials with registration purposes in Brazil are often financially supported by multinational pharmaceutical industries[15,20].

The large number of phase III studies in FUHs suggested that their participation was mostly operational, as opposed to the idea that these trials are necessarily linked to the scientific competence of university hospitals. Brazilian pharmaceutical companies have a limited capacity of promoting all steps (pre-clinical and phases I-II) of technological development and innovation[16], whereas phase III trials have lower technological requirements and involve other competences such as GCP. Clinical investigators in Brazil are usually experienced in complying to these technical guidelines, which is essential to ensure the quality of clinical trial results[22].

Clinical trials are the methodological gold standard in testing the efficacy and safety of products for human health. They are required for the registration and commercialization of health products, being part of the technological innovation process in the health sciences[23]. Hence, these types of studies comprise guidelines and policies related to health, science, technology, and innovation and industrial development[24-26]. From an institutional perspective, clinical trials qualify professionals and research centers, improve assistance, organize health services[27], and provide new therapeutic options[28] even though they are a scientific validation step. The participation of institutions in these studies should, however, be prudent regarding ethical questions on the vulnerability of participants[29], eventual researchers' conflicts of interests[30], and transparency issues[31]. Especially in FUHs, commercial interests in the participation in clinical trials raise concerns regarding their lack of alignment with academic performance[32] and an unsatisfactory institutional financial management[33].

The limitations of this study include, firstly, the lack of information on the trial sponsors, which did not allow a thorough interpretation of our findings. Secondly, we only analyzed trials coordinated by FUHs, and not those in which FUHs were collaborators. Finally, although the data collection was performed several years ago, we believe that extending the study period would not introduce variance that would significantly change our findings.

In summary, we found that FUHs have a leadership role in the conduction of clinical trials in Brazil, but showed heterogeneity regarding their assistance capacities and the number of clinical trials. This could be better understood through studies identifying factors that influence the creation of diverse institutional operational cultures. The predominance of phase III trials may be interpreted as a low use of the scientific

potentiality of these institutions. The promotion of national collaborative studies could help FUHs in the establishment of an effective cooperation network for improving their capacity of conducting clinical trials, especially considering the EpecSUS program.

This article was produced based on a Master's dissertation in Health Innovation and Technology Management presented in 2016 to the Teaching and Research Institute of Hospital Sírio-Libanês.

Acknowledgements

We thank Flávia Sobral from Clinical Research Management at ANVISA and Thais Valadares from the Board of Directors in Attention to Health at EBSERH for their helpful contributions.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Reis AA, Cecílio LC. A política de reestruturação dos hospitais de ensino: notas preliminares sobre os seus impactos na micropolítica da organização hospitalar. *Saude Debate*. 2009;33(81):88-97.

2. Brasil. Presidência da República. *Lei nº 12.550, de 15 de dezembro de 2011*. Autoriza o Poder Executivo a criar a empresa pública denominada Empresa Brasileira de Serviços Hospitalares – EBSERH. Diário Oficial da União [Internet]. 2011 Dec 15 [cited 2019 Nov 1]. Available from: http://www.planalto.gov.br/ccivil_03/_Ato2011-2014/2011/Lei/L12550.htm.

3. Empresa Brasileira de Serviços Hospitalares. *Sobre os hospitais universitários federais* [Internet]. Brasília, DF: EBSERH; 2019 [cited 2019 Nov 1]. Available from: https://www.gov.br/ebserh/pt-br/acesso-a-informacao/hospitais-universitarios-federais/rede-ebserh/mapa-da-rede-ebserh/mapa-da-rede-ebserh-2020.png/view.

4. Brasil. Ministério da Saúde. *Rede Assistencial* [Internet]. Brasília, DF: Ministério da Saúde; 2008 [cited 2019 Nov 15]. Available from: http://www2.datasus.gov.br/DATASUS/index.php?area=0204.

5. Diretório dos Grupos de Pesquisas no Brasil. Lattes. Conselho Nacional de Desenvolvimento Científico e Tecnológico. *Plano tabular* [Internet]. Brasília, DF: CNPq; 2010 [cited 2019 Nov 1]. Available from: http://lattes.cnpq.br/web/dgp/sobre12;jsessionid=RAfY5GjmDLFI8Xccy6cIVAu+.undefined

6. U.S. National Library of Medicine. *Learn about clinical studies* [Internet]. Bethesda: U.S. National Library of Medicine; 2015 [cited 2019 Nov 1]. Available from: https://clinicaltrials.gov/ct2/about-studies/learn

7. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. *Resolução da Diretoria Colegiada – RDC nº 9, de 20 de fevereiro de 2015*. Dispõe sobre o Regulamento para a realização de ensaios clínicos com medicamentos no Brasil [Internet]. Brasília, DF: Anvisa; 2015 [cited 2019 Nov 1]. Available from: https://www.jusbrasil.com.br/diarios/86911532/dou-secao-1-03-03-2015-pg-69

8. Brasil. Ministério da Saúde. Conselho Nacional de Saúde. *Resolução nº 466, de 12 de dezembro de 2012* [Internet]. Brasília, DF: Diário Oficial da União; 2012 [cited 2019 Nov 1]. Available from: http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf

9. U.S. National Library of Medicine. *See studies on map* [Internet]. Bethesda: U.S. National Library of Medicine; 2015 [cited 2019 Nov 1]. Available from: https://clinicaltrials.gov/ct2/search/map/click?map.x=256&map.y=317

10. ISR Reports. *Preview of 2017 CRO market size projection 2016-2021* [Internet]. USA: Raleigh; 2017 [cited 2019 Nov 1]. Available from: https://isrreports.com/wp-content/uploads/2017/03/Preview-2017-CRO-Market-Size-final-1.pdf

11. Brasil. Ministério da Educação. *Portaria Interministerial nº 9, de 13 de agosto de 2014* [Internet]. Brasília, DF: Ministério da Educação; 2014 [cited 2019 Nov 1]. Available from: http://www.lex.com.br/legis_25838627_PORTARIA_INTERMINISTERIAL_N_9_DE_13_DE_AGOSTO_DE_2014.aspx

12. U.S. Food & Drug Administration. *ICH guidance documents* [Internet]. USA: Silver Spring; 2013 [cited 2019 Nov 1]. Available from: http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/guidancesinformationsheetsandnotices/ucm219488.htm

13. Agência Nacional de Vigilância Sanitária (ANVISA). *Consulta de ensaios clínicos autorizados* [Internet]. Brasília, DF: ANVISA; 2014 [cited 2019 Nov 1]. Disponível em: http://www7.anvisa.gov.br/Datavisa/Consulta_Comunicados/Consulta_CE_Autorizados.asp

14. Brasil. Ministério da Saúde. Portal da Saúde SUS. *Tabwin* [Internet]. Brasília, DF: Ministério da Saúde; c2008 [cited 2019 Nov 1]. Available from: http://www2.datasus.gov.br/DATASUS/index.php?area= 060805

15. Quental C, Salles Filho S. Ensaios clínicos: capacitação nacional para avaliação de medicamentos e vacinas. *Rev Bras Epidemiol*. 2006;9(4):408-24.

16. Gomes RP, Pimentel VP, Landim AB, Pieroni JP. *Ensaios clínicos no Brasil* [Internet]. Rio de Janeiro, RJ: Banco Nacional de Desenvolvimento Econômico e Social; 2012 [cited 2019 Nov 1]. Available from: https://web.bndes.gov.br/bib/jspui/handle/1408/1504

17. Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Ministério da Saúde. Rede nacional de pesquisa clínica no Brasil: respostas e redução da dependência estrangeira. *Rev Saude Publica*. 2010;44(3):575-8.

18. Ng SM, Weindling AM. The impact of networks on clinical trials in the United Kingdom. *Trials*. 2009;10(100):1-6.

19. Braend AM, Jensen KB, Klovning A, Straand J. Clinical drug trials in general practice: a 10-year overview of protocols. *Trials*. 2013;14(162):1-10.

20. Zuccheti C, Morrone FB. Perfil da pesquisa clínica no Brasil. *Rev HCPA*. 2012;32(3):340-7.

21. International Federation of Pharmaceutical Manufacturers & Associations. *Facts & Figures 2015* [Internet]. Gênova: EFPIA; 2015

[cited 2015 Mar 25]. Available from: https://www.ifpma.org/wp-content/uploads/2016/02/IFPMA_-_Facts_And_Figures_2015_web.pdf

22. Paschoale HS. *Perfil da pesquisa clínica*: identificação de oportunidades e desafios para o futuro [thesis] [Internet]. São Paulo: Universidade de São Paulo; 2009 [cited 2019 Nov 1]. Available from: https://www.teses.usp.br/teses/disponiveis/5/5147/tde-07122009-182348/publico/HelenaSCavonePaschoale2009.pdf

23. Moreira NV, Almeida FA, Cota M, Sbragia R. Technological innovation in Brazil: a new framework for innovation and management of sectorial funds. *REGE Rev Gestão*. 2007;14:31-44.

24. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia. *Pesquisas estratégicas para o sistema de saúde – PESS* [Internet]. Brasília, DF: Ministério da Saúde; 2011 [cited 2019 Nov 1]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/livro_pesquisas_estrategicas_para_o_sus.pdf

25. Brasil. Ministério da Ciência, Tecnologia e Inovação. *Estratégia Nacional de Ciência, Tecnologia e Inovação 2012-2015*: balanços das atividades estruturantes 2011 [Internet]. Brasília, DF: MCTI; 2012 [cited 2019 Nov 1]. Available from: http://livroaberto.ibict.br/218981.pdf

26. Brasil. Ministério do Desenvolvimento, Indústria e Comércio Exterior. Agência Brasileira de Desenvolvimento Industrial. *Relatório de acompanhamento das agendas estratégicas setoriais* [Internet]. Brasília, DF: ABDI; 2014 [cited 2019 Nov 1]. Available from: https://docplayer.com.br/84529459-Relatorio-de-acompanhamento-das-agendas-estrategicas-setoriais-agosto-2014.html

27. Miyaoka TM, Cesar MB, Laranjeira LN, Guimarães HP, Avezum A. Hospitais envolvidos em pesquisa clínica oferecem melhores resultados aos seus pacientes? *Rev Bras Hipertens*. 2008;15(4):225-7.

28. Dainesi SM, Goldbaum M. Pesquisa clínica como estratégia de desenvolvimento em saúde. *Rev Assoc Med Bras*. 2012;58(1):2-6.

29. Schramm FR, Palacios M, Rego S. O modelo bioético principialista para a análise da moralidade da pesquisa científica envolvendo seres humanos ainda é satisfatório?. *Cien Saude Colet*. 2008;13(2):361-70.

30. Boyd EA, Cho MK, Bero LA. Financial conflict-of-interest policies in clinical research: issues for clinical investigators. *Acad Med*. 2003;78(8):769-74.

31. Ghersi D, Pang T. En route to international clinical trial transparency. *Lancet*. 2008;372(9649):1531-2.

32. Zago MA. A pesquisa clínica no Brasil. *Cien Saude Colet*. 2004;9(2):363-74.

33. Brasil. Tribunal de Contas da União. *Acórdão 2813/2009* [Internet]. Brasília, DF: Tribunal de Contas da União; 2009 [cited 2019 Nov 15]. Available from: https://www.lexml.gov.br/urn/urn:lex:br:tribunal.contas.uniao;camara.2:acordao:2009-06-02;2813

Received: Nov 25, 2019
Accepted: Apr 17, 2020